Factors associated with potential drug–drug interactions in psychiatric inpatients

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ABSTRACT

Objective The aim of this study was to investigate the prevalence and severity of potential drug–drug interactions (pDDIs) in hospitalised patients with major psychiatric disorders and to identify factors associated with their occurrence.

Methods The research was designed as an observational, cross-sectional study conducted at the Clinic for Mental Disorders (CMD) 'Dr. Laza Lazarevic', Belgrade, Serbia. Medscape, Epocrates and Lexicomp bases were used to detect potential drug interactions among inpatients. Multivariate regression analysis was used to reveal risk and protective factors associated with the number of pDDIs.

Results The study included 511 patients, average age 44.63±11.81 years. The average number of pDDIs per patient ranged from 5.9±4.7 (Medscape) to 8.2±5.4 (Epocrates) and 8.5±5.1 (Lexicomp). The following risk factors were identified by all three interaction checkers used: C-reactive protein, number of pharmacological subgroups, number of prescribed drugs, antibiotics, antacids, vitamins, number of associated comorbidities, route, form and dose of the drug.

Conclusions When making clinical decisions to reduce drug problems, including DDIs, one should consult several interaction databases, which should be reviewed by a multidisciplinary team consisting of an experienced clinical pharmacist, physician, nurse, and so on.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ The most common risk factors for potential drug–drug interactions (pDDIs) in psychiatric patients are age, number of drugs and gender.

WHAT THIS STUDY ADDS

⇒ Drug- and patient-related risk factors for pDDIs include C-reactive protein, number of pharmacological subgroups, number of prescribed drugs, antibiotics, antacids, vitamins, number of associated comorbidities, route, form and dose of the drug.

⇒ The most frequently detected pDDI was between diazepam and olanzapine.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Detected risk factors can be used to define the subpopulation of patients at high risk for interactions, as well as to plan the introduction of monitoring for early detection of interactions.

INTRODUCTION

Patients with mental illness frequently have comorbidities like cardiovascular disease, diabetes, obesity, asthma, epilepsy and cancer. For this reason, many patients with psychiatric disorders use multiple medications. As the number of prescriptions increases, so does the possibility of adverse drug reactions, especially those caused by drug–drug interactions (DDIs). The incidence of potential drug–drug interactions (pDDIs) with clinical significance in hospitalised patients ranges from 27.8% to 51.4%.[1] Age, multiple prescriptions, gender and comorbidities are short-listed as the most common risk factors for pDDIs in psychiatric patients.[2] Although numerous articles about pDDIs have been published, few studies have dealt with DDIs in psychiatric departments. A study conducted in England with 323 psychiatric patient participants found that 20% of them had pDDIs involving drug metabolism by CYP2D6 and CYP3A4 enzymes.[3] A study from Brazil, in which 430 primary care psychiatric patients participated, revealed pDDIs in 58.4% of all cases, while age and number of drugs were highlighted as risk factors.[4] A study conducted in Pakistan involving 450 psychiatric patients showed that the number of drugs, the length of hospitalisation and the age of the patients were associated with pDDIs.[5] A similar conclusion was reached in a study from Saudi Arabia, where in a sample of 270 patients it was shown that advanced age and multiple prescriptions promote the emergence of pDDIs.[6] However, previous studies which examined the risk factors for the occurrence of interactions did not pay particular attention to the severity of interactions, but concentrated mostly on risk factors for DDIs in general.

The aim of this study was to investigate the prevalence and severity of pDDIs in hospitalised patients with major psychiatric disorders and to identify factors associated with their occurrence. Identification of patients with high pDDI-adverse event risk might facilitate the recognition of pDDI-related harm and improve the use of electronic databases in clinical practice.

METHODS

This observational, unsponsored, cross-sectional study was conducted at the Clinic for Mental Disorders (CMD) "Dr. Laza Lazarevic" in Belgrade, Serbia between 1 January 2019 and 30 June 2020. Information was gleaned from the files of hospitalised patients suffering from major psychiatric illnesses.

The study included patients having one of the following diagnoses: Schizophrenia (F 20.0–20.9), Bipolar Affective Disorder (F 31.0–31.9) and Depression (F 32.0–32.9). The other inclusion

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criteria used in the study were: hospitalisation for at least 48 hours at the clinic, age over 18 years, and being prescribed at least two drugs. The following patients were excluded from the study: those below 18 years of age, pregnant women, and patients refusing to participate in the study. Prior to its onset, the study was approved by the Ethics Committee of the CMD "Dr. Laza Lazarevic".

The following data were extracted from the patient files: the number and names of prescribed drugs, duration of hospitalisation, sociodemographic characteristics, habits and details about the patients' current conditions (including comorbidities). The drugs were also classified according to the Anatomical Therapeutic Chemical Classification codes (ATC). The extracted data were transformed to the following variables: age, gender, length of hospitalisation, main diagnosis, heart rate, systolic and diastolic blood pressure, laboratory parameters (acidum uricum (AU), creatine kinase (CK), urea, serum creatinine, erythrocyte sedimentation rate, white and red blood cell count, platelet count, haemoglobin, potassium, sodium, iron, blood glucose level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, total protein, C-reactive protein (CRP), total cholesterol, triglycerides, habits (smoking, alcohol, psychoactive substances), comorbidities (diabetes, hypertension, hyperlipidemia, especially presence of dementia, delirium, heart failure, renal failure, liver cirrhosis, chronic obstructive pulmonary disease (COPD), asthma, arrhythmias, cerebrovascular diseases, malignant diseases), Charlson Comorbidity Index (CCI), pharmacotherapy data including all drugs prescribed to each patient (number of prescribed drugs, number of different therapeutic subgroups prescribed at second level of ATC classification), prescribed antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, antiepileptics, anticholinergics, dopaminergics, antiarrhythmic drugs, antibiotics, antidiabetics, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, corticosteroids, statins, antihistamines, bronchodilators, laxatives, thyroid disease therapy, vitamins, proton-pump inhibitors, antihypertensives, diuretics or nitrates, tetanus vaccine, drug allergy noted in the medical documentation, and number and description of the pDDI.

To identify pDDIs, three web-based interaction checkers were used: Medscape, Epocrates, and Lexicomp. The potential severity of discovered pDDIs was classified as follows: Medscape classified pDDIs as contraindicated, serious—use alternative, monitor closely, and minor; Epocrates recognised pDDIs as avoid/use alternative, monitor/modify therapy, and caution advised; and the Lexicomp checker rated pDDIs based on potential risk: classes X (avoid combination), D (consider therapy modification), C (monitor therapy) and B (no action needed). The Lexicomp monographs were used to extract data on proposed mechanisms, consequences and reliability of a pDDI. Possible consequences were categorised as: minor (effects would be considered tolerable in most cases—no need for medical intervention); moderate (medical intervention needed to treat effects; effects do not meet criteria for major); and major (effects may result in death, hospitalisation, permanent injury, or therapeutic failure). Depending on the type and quality of published evidence for a certain pDDI, the reliability was defined as poor, fair, good or excellent.

All statistical calculations were made using the Statistical Programme for Social Sciences (SPSS version 18). Continuous variables were first described by measures of central tendency (mean and median) and measures of dispersion (standard deviation (SD) and range). Categorical variables were presented by frequencies and percentages (%). The influence of possible predictors and confounders on outcomes (the number of interactions, in total and according to the types discovered by different databases) was examined by multiple linear regression, after confirming that the following assumptions were met: linear relationship between predictors and outcome, normal distribution of residuals, homoscedascity and absence of significant collinearity. A 'backward selection' technique was used to build the final models. Analysis of variance (F value) and percentage of outcome (number of DDIs per patient) variability explained (R2) were used to assess the statistical validity of the regression models of potential risk factors on the number of DDIs per patient. They were assessed by their B coefficients within the regression equation, including confidence intervals (CIs).

RESULTS

The study included 511 patients (285 males and 226 females) who were hospitalised in the CMD 'Dr. Laza Lazarevic', Belgrade, during the study period. The average age of the patients was 44.63±11.81 years. Characteristics of the patients in detail (sociodemographic characteristics, laboratory parameters, comorbidities, prescribed pharmacotherapy) are shown in table 1.

The average number of pDDIs detected by each of the interaction checkers (Medscape, Epocrates and Lexicomp) is shown in table 2.

The largest number of pDDIs was detected by the Lexicomp database. The five most frequent DDIs, with the description, are shown in table 3 for each of thee interaction checkers.

The risk factors with significant influence on the number of pDDIs according to the drug checker used and degree of severity are presented in tables 4–6).

Approximately 20% of pDDIs belong to groups X (avoid combination) and D (consider therapy modification) according to the Lexicomp database; the same percentage according to the Epocrates database formed groups Contraindicated and Avoid/use alternative. Conversely, the frequency of more severe pDDIs in the groups Contraindicated and Serious – Use alternative according to the Medscape database was significantly lower (about 6%).

In the final multiple linear regression models, predictor variables with significant influence on the number of pDDIs according to the drug checker used and the degree of severity were separated. According to the Medscape interaction checker, sixteen variables positively (risk factors) and seven negatively (protective factors) influenced the number of DDIs. Twenty-seven risk factors were identified in the Epocrates database, but only five protective factors. According to the Lexicomp base, fourteen variables acted as risk factors and thirteen variables as protective factors in relation to the number of DDIs.

Our study showed that risk factors for pDDIs detected by the Medscape drug checker were CRP, number of pharmacological/therapeutic subgroups (second level of ATC classification), antiepileptic drugs, anticholinergics, antihypertensives, statins, antibiotic drugs, antacids, laxatives, tetanus vaccine, vitamins, number of associated comorbidities, heart attack, liver disease, the route and dose of the drug increased the manifestation of the interaction. Protective factors according to this database were age, red blood cells, erythrocyte sedimentation, antidiabetic drugs, diagnosis, number of diagnoses, urinary tract infection and hypertension.

Analysis of pDDIs identified by the Epocrates database showed that gender, platelet count, CRP, number of pharmacological/

Table 1 Characteristics of the study sample (n=511)

Variable	Mean±SD or number	Median, IQR or number (%)
Age (years)	44.63±11.81	46.00 (18)
Gender (male/female)	285/226	55.8%/44.2%
Diagnosis		
Schizophrenia	257	50.3%
Bipolar affective disorder	127	24.9%
Depression	127	24.9%
Length of hospitalisation (days)	32.26±11.64	31.00 (14)
Hospitalisation number		
First	46	9%
Second	60	11.7%
Third	24	4.7%
>Third	381	74.6%
White blood cell count ($x10^9$/L)	7.02±2.21	6.70 (2.7)
Red blood cell count ($x10^{12}$/L)	4.58±0.51	4.57 (0.64)
Platelet count ($x10^9$/L)	252.45±69.21	248.00 (99)
Haemoglobin (g/L)	139.20±16.45	140.00 (18)
Erythrocyte sedimentation rate (mm/h)	15.20±11.88	12.00 (13)
CRP (mg/L)	7.13±12.67	4.00 (4.2)
Glucose (mmol/L)	5.05±1.07	4.90 (0.9)
Urea (mmol/L)	4.39±3.24	4.10 (2)
Serum creatinine (µmol/L)	85.11±16.33	85.00 (99)
Uric acid (µmol/L)	288.61±127.55	278.00 (118)
Total proteins (g/L)	70.11±6.30	70.00 (7)
Total bilirubin (µmol/L)	8.63±5.68	7.30 (5)
Total cholesterol (mmol/L)	5.15±1.27	5.00 (7.1)
Triglycerides (mmol/L)	1.74±1.04	1.48 (1.26)
AST (IU/L)	21.26±13.35	18.00 (11)
ALT (IU/L)	24.85±16.75	20.00 (14)
ALP (IU/L)	73.63±24.18	69.00 (29)
GGT (IU/L)	29.99±22.08	23.00 (19)
CK (IU/L)	211.08±314.10	102.00 (131)
Potassium (mmol/L)	4.38±0.42	4.37 (0.47)
Sodium (mmol/L)	140.61±5.60	141.30 (4)
Iron (µmol/L)	15.15±6.59	14.30 (8.2)
Number of diagnoses	2.52±1.32	2.00 (2)
Number of associated comorbidities	0.59±0.77	0.00 (1)
Charlson Comorbidity Index (CCI)	1.08±1.31	1.00 (2)
Systolic blood pressure (mmHg)	128.70±19.66	130.00 (25)
Diastolic blood pressure (mmHg)	81.40±11.71	82.00 (15)
Heart rate (beats/min)	77.85±11.60	77.00 (18)
Anaemia (yes/no)	49/462	9.6%/90.4%
Leucopenia (yes/no)	12/499	2.3%/97.7%
Dyslipidaemia (yes/no)	76/435	14.9%/85.1%
Hypothyroidism (yes/no)	26/485	5.1%/94.9%
Urinary tract infection (yes/no)	65/446	12.7%/87.3%
Hypertension (yes/no)	125/386	24.5%/72.8%
Constipation (yes/no)	50/461	9.8%/90.2%
Respiratory infection (yes/no)	109/401	21.3%/78.5%
Heart attack (yes/no)	17/490	3.3%/95.9%
Congestive heart failure (yes/no)	42/469	8.2%/91.8%
Cerebrovascular accident (yes/no)	16/495	3.1%/96.9%
Dementia 0(yes/no)	17/494	3.3%/96.7%
COPD (yes/no)	26/485	5.1%/94.9%
Rheumatic diseases (yes/no)	20/491	3.9%/96.1%
Peptic ulcer disease (yes/no)	25/486	4.9%/95.1%
Liver disease (yes/no)	20/491	3.9%/96.1%
Diabetes mellitus (yes/no)	49/462	9.6%/90.4%
Renal failure (yes/no)	23/488	4.5%/95.5%
Tumour (yes/no)	16/495	3.1%/96.9%
Smoker (yes/no)	338/173	66.1%/33.9%
Alcoholic (yes/no)	90/421	17.6%/82.4%
Psychoactive substances (yes/no)	54/456	10.6%/89.2%
Allergy (yes/no)	54/456	10.6%/89.2%
Number of prescribed drugs	6.71±2.68	6.00,(3)
Number of different therapeutic subgroups prescribed (second level of ATC classification)	4.93±2.17	5.00,(3)
Analgesics (yes/no)	24/487	4.7%/95.3%
Antacids (yes/no)	69/442	13.5%/86.5%
Antiarrhythmic drugs (yes/no)	53/458	10.4%/89.6%
Antibiotics (yes/no)	170/341	33.3%/66.7%
Antiepileptics (yes/no)	426/85	83.4%/16.6%
Anticholinergics (yes/no)	91/420	17.8%/82.2%
Anticoagulants (yes/no)	41/470	8%/92%
Antidepressants (yes/no)	230/281	45%/55%
Antidiabetics (yes/no)	48/463	9.4%/90.6%
Antihypertensives (yes/no)	122/389	23.9%/76.1%
Antihistamines (yes/no)	29/482	5.7%/94.3%
Antipsychotics (yes/no)	499/12	97.7%/2.3%
Anxiolytics (yes/no)	469/42	91.8%/8.2%
Bronchodilators (yes/no)	38/473	7.4%/92.6%
Corticosteroids (yes/no)	44/467	8.6%/91.4%
Dementia drugs (yes/no)	17/494	3.3%/96.7%
Diuretics (yes/no)	99/412	19.4%/80.6%
Dopaminergic drugs (yes/no)	11/500	2.2%/97.8%
Hypnotics and sedatives (yes/no)	201/309	39.3%/60.5%
Laxatives (yes/no)	50/461	9.8%/90.2%
Nonsteroidal anti-inflammatory drugs (yes/no)	97/414	19%/81%
Statins (yes/no)	63/448	12.3%/87.7%
Tetanus vaccine (yes/no)	23/488	4.9%/95.1%
Thyroid disease therapy (yes/no)	25/486	23.%/76.3%
Vitamins (yes/no)	121/390	4.5%/95.5%

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATC ATC classification, Anatomical Therapeutic Chemical Classification; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GGT, gamma-g transferase.

therapeutic subgroups (second level of ATC classification), anticholinergic drugs, analgesics, statins, antibiotic drugs, antacids, antihistamines, bronchodilators, NSAIDs, laxatives, thyroid disease therapy, vitamins, respiratory infection, number of associated comorbidities, heart attack, cerebrovascular accident, dementia, rheumatic diseases, liver disease, diabetes mellitus, renal failure, and the route, form and dose of the drug increase the risk of DDIs. Erythrocyte sedimentation, ALP, number of diagnoses, hypnotics, sedatives, and antidepressants were negatively correlated with the number of DDIs and therefore behaved as protective factors. CRP, glucose, number of prescribed drugs, anticoagulants, antibiotic drugs, antacids, NSAIDs, tetanus vaccine, vitamins, dyslipidaemia, number of associated comorbidities, route, form, and dose of the drug are the Lexicomp base risk factors that increase the number of pDDIs. Protective factors included white blood cells, triglycerides, antipsychotics,

Table 2 Number of potential drug–drug interactions according to the interaction checker per patient

Type of interaction	Mean±SD	Median (IQR)
Medscape total	5.93±4.78	5.00 (5)
Contraindicated	0.01±0.20	0.00 (0)
Serious - use alternative	0.36±0.86	0.00 (0)
Monitor closely	4.77±3.84	4.00 (5)
Minor	0.80±1.19	0.00 (1)
Epocrates total	8.21±5.43	7.00 (5)
Contraindicated	0.07±0.44	0.0 (0)
Avoid/use alternative	1.60±1.84	1.00 (3)
Monitor/modify therapy	5.00±4.45	4.00 (4)
Caution advised	1.63±1.61	1.00 (3)
Lexicomp total	8.58±5.16	7.00 (6)
X-avoid combination	0.64±0.93	0.00 (1)
D-consider therapy modification	1.09±1.38	1.00 (2)
C-monitor therapy	6.20±4.18	5.00 (5)
B-no action needed	0.67±0.98	0.00 (1)

hypnotics, sedatives, antidepressants, antiepileptics, dopaminergic drugs, antiarrhythmic, antihistamine drugs, number of diagnoses, urinary tract infection, hypertension and allergy.

The following risk factors were identified by all three interaction checkers used: CRP, number of pharmacological/therapeutic subgroups (second level of ATC classification), number of prescribed drugs, antibiotics, antacids, vitamins, number of associated comorbidities, route, form and dose of the drug.

DISCUSSION

The quality of the information within DDI monographs differs between drug interaction checkers. Important features of electronic databases are sensitivity (ability to identify clinically significant DDIs) and specificity (neglect of DDIs that are not clinically significant). The Lexicomp-Interact and Epocrates databases were rated as the most accurate, and Lexicomp-Interact and Micromedex, respectively, were rated as the best bases in terms of relevance, completeness and ease of use of applications.[7] Direct comparison of interaction checkers found that Lexicomp has better sensitivity than Medscape (87% vs 69%), while the specificity was in favour of Medscape (92% vs 88%).[8] The Lexicomp database, in contrast to the Medscape and Epocrates interaction search databases, provides more information on potential interactions and their characteristics (the five most common severe DDIs in the Lexicomp database are caused by the drug's route of administration). Previous studies of Medscape and Epocrates found that the expected onset of potential interactions was not specified in most cases, and most potential interactions were not satisfactorily supported by scientific evidence, most likely due to the fact that there is no clear evidence for most interactions or no clinical controlled studies that could confirm their existence.

Another disadvantage of Medscape and Epocrates databases is that they do not have in their databases some of the drugs present in the Lexicomp database, which is one of the reasons for the smaller number of interactions identified by searching these databases. These are the following drugs: mianserin, salbutamol, paracetamol, cephalexin, bromazepam, nitrazepam, levomepromazine and biperiden.

Numerous other studies have found a strong link between pDDIs and an increased number of drugs.[4 5 9] In a study conducted in Mexico, 81.4% of patients were prescribed six or more drugs and were five times more likely to suffer adverse effects while 14.2% had polypharmacy while receiving antipsychotics and had more than twice the risk of presenting with extrapyramidal symptoms.[10] One of the most recent studies in the United Arab Emirates proved that the number of drugs and polypharmacy significantly predicted pDDIs.[11]

Although the association between length of hospitalisation and total number of pDDIs was not previously shown for psychiatric patients in a number of studies, in our study the association was significant for contraindicated and avoided pDDIs. The same was shown by the study conducted in Pakistan.[4]

Table 3 Description and frequency of selected Contraindicated, Avoid/use alternative (Medscape and Epocrates databases) and Avoid combination-X (Lexicomp database) potential drug–drug interations

Drug combination	Description	Number (%) of patients
Medscape		
contraindicated	Erythromycin base will increase the level or effect of simvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism	1 (0.03%)
1.Erythromycin- simvastatin		19 (0.63%)
Serious – use alternative	Carbamazepine will decrease the level or effect of diazepam by affecting hepatic/intestinal enzyme CYP3A4 metabolism	17 (0.56%)
1.Carbamazepine-diazepam		7 (0.23%)
2.Carbamazepine-clozapine	Carbamazepine will decrease the level or effect of clozapine by affecting hepatic/intestinal enzyme CYP3A4 metabolism	3 (0.1%)
1. Erythromycin- diazepam	Erythromycin base will increase the level or effect of diazepam by affecting hepatic/intestinal enzyme CYP3A4 metabolism	
2. Azithromycin-dalteparin	Azithromycin increases effects of dalteparin by decreasing metabolism	
Epocrates contraindicated	Contraindicated for solid potassium dose forms; use alternative dose forms: combination may delay solid potassium passage through gastrointestinal (GI) tract, increasing risk of ulcerative/stenotic lesions (anticholinergics slow GI transit, increasing local exposure to high potassium concentration)	
1. Olanzapine-potassium chloride		8 (0.19%)
2. Haloperidol-potassium chloride		6 (0.14%)
3.Clozapine-potassium chloride	Contraindicated if seizure disorder use; otherwise, use alternative or monitor respiratory rate; combination may alter seizure control; may increase risk of profound central nervous system (CNS) and respiratory depression, psychomotor impairment	4 (0.10%)
1. Lorazepam - metoclopramide		3 (0.07%)
2. Midazolam- metoclopramide		3 (0.07%)
Lexicomp		
Avoid combination	Avoid concomitant use of parenteral benzodiazepines and intramuscular (IM) olanzapine due to risks of additive adverse effects (eg,cardiorespiratory depression, excessive sedation). Additive pharmacologic effects might also be expected with oral use of these agents, but specific recommendations for management are lacking	48 (9.39%)
1.Diazepam-olanzapine		36 (7.04%)
2.Midazolam-olanzapine	Consider alternatives to this combination whenever possible. If combined, monitor closely for signs and symptoms of gastrointestinal hypomotility (eg, constipation, nausea, abdominal distension or pain, vomiting) and consider prophylactic laxative treatment	32 (6.26%)
3.Lorazepam-olanzapine		27 (5.28%)
4.Bromazepam-olanzapine		25 (4.89%)
5.Clozapine-olanzapine		

Table 4 Factors associated with potential drug–drug interactions detected by the Medscape drug checker according to multiple linear regression model

Variable	B	P value	95% CI
Medscape total interactions			
Age	−0.049	0.003	−0.081 to −0.017
Red blood cells	−0.678	0.031	−1.294 to −0.063
Erythrocyte sedimentation rate	−0.038	0.013	−0.069 to −0.008
C-reactive protein	0.030	0.034	0.002 to 0.057
Diagnosis	−0.642	0.005	−1.087 to −0.196
Number of pharmacological/ therapeutic subgroups (second level of ATC classification)	1.577	0.000	1.327 to 1.827
Antiepileptic drugs	1.204	0.003	0.912 to 1.996
Anticholinergics	1.121	0.005	0.348 to 1.893
Antihypertensives	2.102	0.005	0.623 to 3.582
Statins	1.671	0.001	0.693 to 2.665
Antibiotic drugs	1.114	0.006	0.325 to 1.903
Antacids	2.831	0.000	1.847 to 3.814
Laxatives	1.264	0.013	0.272 to 2.256
Tetanus vaccine	2.226	0.002	0.841 to 3.611
Vitamins	1.751	0.000	0.974 to 2.528
Number of diagnoses	−0.611	0.012	−1.086 to −0.135
Urinary tract infection	−1.858	0.000	−2.803 to −0.912
Hypertension	−1.548	0.044	−3.055 to −0.042
Number of associated comorbidities	0.916	0.002	0.335 to 1.497
Heart attack	2.153	0.001	0.907 to 3.400
Liver disease	1.966	0.011	0.450 to 3.483
Number of interactions in which the route of the drug increased the manifestation of the interaction	0.722	0.000	0.357 to 1.087
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.555; F (p)=21.471 (0.000*)	0.767	0.027	0.085 to 1.449
Contraindicated			
Length of hospitalisation (days)	0.002	0.022	0.000 to 0.003
Antibiotic drugs	0.041	0.025	0.005 to 0.077
Antidiabetic drugs	−0.137	0.000	−0.203 to −0.072
Charlson Comorbidity Index (CCI)	−0.026	0.001	−0.041 to −0.010
Smoker	0.046	0.010	0.011 to 0.082
Tumour	−0.162	0.002	−0.263 to −0.061
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.101; F (p)=6.689 (0.000)*	0.090	0.000	0.051 to 0.129
Serious – use alternative			
Gamma-glutamyl transferase (GGT)	0.004	0.008	0.001 to 0.008
Number of pharmacological/ therapeutic subgroups (second level of ATC classification)	0.095	0.000	0.052 to 0.138
Dopaminergic drugs	−1.347	0.000	1.816 to −0.878
Antihypertensives	0.241	0.029	0.025 to 0.458
Diuretics	−0.243	0.036	−0.469 to −0.016
Anticoagulants	−0.375	0.006	0.643 to −0.107
Antacids	0.258	0.032	0.023 to 0.494
Vitamins	0.270	0.003	0.091 to 0.449
Urinary tract infection	−0.329	0.001	−0.529 to −0.129
Number of associated comorbidities	0.608	0.000	0.353 to 0.863
Heart attack	0.608	0.001	0.236 to 0.981
Cerebrovascular accident	0.851	0.000	0.395 to 1.306
Dementia	0.782	0.001	0.337 to 1.226
Chronic obstructive pulmonary disease (COPD)	0.749	0.000	0.364 to 1.134
Rheumatic diseases	0.653	0.002	0.247 to 1.058
Peptic ulcer disease	0.554	0.007	0.155 to 0.953
Liver disease	1.111	0.000	0.673 to 1.550
Diabetes mellitus	0.745	0.000	0.412 to 1.078
Renal failure	0.867	0.000	0.464 to 1.270
Tumour	0.448	0.046	0.008 to 0.889
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.310; F (p)=10.139 (0.000)*	0.373	0.000	0.216 to 0.530

*Statistically significant.
ATC, Anatomical Therapeutic Chemical; B, unstandardised coefficient; p, statistical significance.

The risks from DDIs are substantially increased in patients with more comorbidities, and the same was shown by the study of Wolff *et al*.[12] With increased CRP values, antibiotic administration was more frequent, increasing the risk of pDDIs. It is not surprising that antibiotics, NSAIDs, analgesics, statins and anticoagulants were risk factors for pDDIs, since these drugs have multiple mechanisms available to interact both pharmacokinetically and pharmacodynamically with drugs from other groups. For antacids, laxatives and vitamins, the presence of pharmacokinetic interactions at the level of absorption and distribution is characteristic (due to the presence of large cations) and has been described in many studies.[13 14] Also, tetanus vaccines, bronchodilators and drugs in thyroid therapy were identified as risk factors for pDDIs by other authors.[15 16]

Antihypertensives and antiarrhythmic drugs are specific risk factors for DDIs because the most common problems produced by these interactions are related to cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and increased exposure due to inhibition of cytochrome P450 2D6 (CYP2D6).[17 18] In our study, antiarrhythmics had a protective effect on pDDIs. An increased risk of adverse drug reactions was found with the simultaneous use of anticholinergics and several QT interval prolonging drugs.[19 20] The same conclusion was found in our study, where anticholinergics behaved as risk factors for potential DDIs.

Contradictory results concerning the effects of antiepileptics and antihistamines on pDDIs were obtained from analysing interactions by the three interaction checkers. According to Epocrates and Medscape, these two drug groups increased the risk of pDDIs, but according to the Lexicomp database, they reduced the risk. According to the Lexicomp database, antipsychotics, antiepileptics, hypnotics, sedatives and antidepressants had protective effects, which seems paradoxical. However, such a result can be explained by the fact that a large proportion of patients were taking these drugs, which introduced an error in the models. Other studies, where these drugs were not so commonly prescribed as to psychiatric patients, showed the opposite: individuals whose prescriptions contained antidepressants, antipsychotics or antiepileptics had a higher risk of pDDIs.[10 21]

Monographs (Dependencies) for certain DDIs also list specific factors of the patient or drug in which the risk of manifestation of interactions is increased, that is, the conditions under which it is considered that their manifestation will occur. It was found

Table 5 Factors associated with potential drug–drug interactions detected by Epocrates drug checker

Variable	B	P value	95% CI
Epocrates total interactios			
Gender (male/female)	1.071	0.000	0.510 to 1.633
Platelet	0.004	0.037	0.000 to 0.008
Erythrocyte sedimentation rate	−0.035	0.018	−0.064 to −0.006
C-reactive protein	0.032	0.016	0.006 to 0.058
Alkaline phosphatase	−0.018	0.002	−0.029 to −0.007
Diagnosis	−0.560	0.009	−0.979 to −0.141
Number of pharmacological/ therapeutic subgroups (second level of ATC classification)	2.161	0.000	1.956 to 2.366
Hypnotics and sedatives	−0.631	0.033	−1.211 to −0.050
Antidepressants	−1.148	0.001	−1.838 to −0.458
Anticholinergic drugs	2.266	0.000	1.544 to 2.987
Analgesics	1.632	0.017	0.295 to 2.969
Statins	2.641	0.000	1.705 to 3.576
Antibiotic drugs	0.934	0.034	0.073 to 1.795
Antacids	3.162	0.000	2.223 to 4.102
Antihistamines	1.898	0.003	0.640 to 3.157
Bronchodilators	2.937	0.000	1.728 to 4.146
Nonsteroidal anti-inflammatory drugs (NSAIDS)	0.785	0.037	0.049 to 1.520
Laxatives	1.993	0.000	1.045 to 2.941
Thyroid disease therapy	2.199	0.001	0.960 to 3.438
Vitamins	3.019	0.000	2.282 to 3.755
Respiratory infection	0.962	0.034	0.073 to 1.852
Number of associated comorbidities	1.575	0.000	0.911 to 2.240
Heart attack	1.754	0.006	0.501 to 3.007
Cerebrovascular accident	1.826	0.043	0.059 to 3.592
Dementia	3.377	0.000	1.720 to 5.034
Rheumatic diseases	2.736	0.000	1.262 to 4.210
Liver disease	1.990	0.009	0.497 to 3.482
Diabetes mellitus	2.764	0.000	1.668 to 3.860
Renal failure	3.223	0.000	1.789 to 4.657
Number of interactions in which the route of the drug increased the manifestation of the interaction	0.632	0.000	0.287 to 0.977
Number of interactions in which the form of the drug increased the manifestation of the interaction	0.625	0.000	0.296 to 0.955
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.694; F (p)=34.918 (0.000)*	1.328	0.000	0.761 to 1.894
Contraindicated			
Sodium	−0.007	0.024	−0.124 to −0.001
Antiepileptics drugs	−0.104	0.036	−0.201 to −0.207
Diuretics	−0.180	0.000	−0.273 to −0.086
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.112; F (p)=11.652 (0.000)*	0.147	0.001	0.062 to 0.232
Avoid – use alternative			
Gender (male/female)	0.341	0.003	0.116 to 0.565
Uric acidi	0.001	0.001	0.001 to 0.002
Number of pharmacological/ therapeutic subgroups (second level of ATC classification)	0.160	0.000	0.092 to 0.229
Length of hospitalisation (days)	0.019	0.000	0.009 to 0.030
Hypnotics and sedatives	−1.853	0.000	−2.090 to −1.617
Dopaminergic drugs	−1.359	0.001	−2.161 to −0.558
Nonsteroidal anti-inflammatory drugs (NSAIDS)	0.515	0.001	0.206 to 0.825
Statins	0.451	0.011	0.105 to 0.797
Cerebrovascular accident	0.791	0.012	0.175 to 1.407
Dementia	0.808	0.013	0.171 to 1.444
Rheumatic diseases	0.647	0.028	0.071 to 1.224
Liver disease	0.616	0.035	0.042 to 1.189
Diabetes mellitus	0.399	0.037	0.023 to 0.774
Number of interactions in which the route of the drug increased the manifestation of the interaction	0.773	0.000	0.626 to 0.920
Number of interactions in which the form of the drug increased the manifestation of the interaction	−0.382	0.000	−0.519 to −0.244
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.547; F (p)=33.345 (0.000)*	−0.296	0.034	−0.570 to −0.022

*Statistically significant.
ATC, Anatomical Therapeutic Chemical; B, unstandardised coefficient; p, statistical significance.

that the most common condition in which the manifestation of interactions depends in patients with psychiatric disorders is the route of drug administration, in slightly fewer than 10% of patients.

The protective effect of drug allergy status and the number of diagnoses a patient has against pDDIs could be explained by increased attention of prescribers to all aspects of drug therapy when prescribing to such patients. Although other studies have shown that the number of diagnoses increases with the number of pDDIs, this may not hold for psychiatric patients in hospital settings.[22] Some studies have shown that age is a significant risk factor for pDDIs,[2 6 12] while some have not confirmed this association.[23 24] Our study showed that age is a protective factor, which can be explained by greater care and more detailed analysis of therapy in elderly patients because they usually have more comorbidities, resulting in more drugs and an increased risk of potential interactions between them.[21] In terms of gender, some studies have not found a significant association,[9 23 24] while others have found a significant influence of female[21] or male sex.[2 25] In this study, the risk of having a greater number of potential interactions in major psychiatric treatment disorders was higher in men.

The associated comorbidities that were the most common in the study sample were hypertension (25%), hyperlipidemia (15%) and diabetes mellitus (about 10%). The most common associated diseases were respiratory and urinary tract infections. Similar associations were found in a study conducted in Germany.[26] The general presence of comorbidities increases the risk of drug interactions, but not all comorbidities are positively correlated. Hypertension and urinary tract infection

Table 6 Factors associated with potential drug–drug interactions detected by Lexicomp drug checker

Variable	B	P value	95% CI
Lexicomp total interactions			
White blood cells	−0.151	0.006	−0.260 to −0.043
C-reactive protein	0.020	0.046	0.000 to 0.039
Glucose	0.325	0.003	0.109 to 0.540
Triglycerides	−0.272	0.034	−0.524 to −0.021
Number of prescribed drugs	1.860	0.000	1.662 to 2.059
Antipsychotics	−1.627	0.036	−3.145 to −0.108
Hypnotics and sedatives	−0.649	0.012	−1.153 to −0.145
Antidepressants	−1.275	0.000	−1.879 to −0.670
Antiepileptics	−0.636	0.047	−1.265 to −0.008
Dopaminergic drugs	−2.681	0.001	−4.283 to −1.078
Antiarrhythmic drugs	−0.865	0.031	−1.653 to −0.078
Anticoagulants	1.729	0.000	0.839 to 2.620
Antibiotic drugs	1.262	0.000	0.617 to 1.907
Antacids	2.558	0.000	1.735 to 3.381
Antihistamines	−1.120	0.032	−2.141−−0.100
Nonsteroidal anti-inflammatory drugs (NSAIDS)	1.165	0.000	0.534 to 1.796
Tetanus vaccine	1.566	0.006	0.448 to 2.684
Vitamins	1.910	0.000	1.278 to 2.542
Number of diagnoses	−1.306	0.000	−1.695 to −0.918
Dyslipidaemia	1.332	0.001	0.533 to 2.130
Urinary tract infection	−0.861	0.029	−1.631 to −0.090
Hypertension	−1.301	0.000	−1.970 to −0.631
Number of associated comorbidities	0.838	0.000	0.410 to 1.266
Allergy	−1.276	0.001	−1.992 to −0.560
Number of interactions in which the route of the drug increased the manifestation of the interaction	0.878	0.000	0.584 to 1.172
Number of interactions in which the form of the drug increased the manifestation of the interaction	0.724	0.000	0.447 to 1.001
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.767; F (p)=51.91 (0.000)*	1.328	0.000	0.761 to 1.894
X-avoid combination			
White blood cell count	0.033	0.019	0.005 to 0.060
Glucose	0.062	0.044	0.123 to −0.002
Antipsychotic drugs	−0.229	0.040	−0.447 to −0.010
Anticholinergic drugs	0.204	0.010	0.048 to −0.360
Anticoagulant drugs	0.356	0.003	0.118 to 0.593
Antibiotic drugs	0.276	0.004	0.091 to 0.462
Antacid drugs	−0.244	0.001	−0.435 to −0.052
Antidiabetic drugs	0.258	0.037	0.016 to 0.501
Antihistamines	0.500	0.001	0.215 to 0.785
Bronchodilators	−0.640	0.003	−1.056 to −0.223
Respiratory infection	−0.351	0.001	−0.557 to −0.144
Number of associated comorbidities	0.159	0.033	0.013 to 0.305
Chronic obstructive pulmonary disease (COPD)	−0.554	0.028	−1.047 to −0.061
Renal failure	0.309	0.047	0.004 to 0.613
Allergy	−0.253	0.010	−0.443 to −0.062
Number of interactions in which the route of the drug increased the manifestation of the interaction	0.594	0.000	0.520 to 0.668
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.489; F (p)=22.1 (0.000)*	0.145	0.048	0.001 to 0.290
D-consider therapy modification			
Total bilirubin	−0.017	0.047	−0.034 to −0.000
Number of pharmacological/ therapeutic subgroups (second level of ATC classification)	0.180	0.000	0.103 to 0.257
Hypnotics and sedatives	−0.243	0.023	−0.452to −0.033
Dopaminergic drugs	−0.976	0.005	−1.657 to −0.295
Statins	0.955	0.006	0.282 to 1.628
Antacids	0.616	0.000	0.285 to 0.958
Diagnosis number	−0.246	0.000	−0.382 to −0.111
Dyslipidaemia	−1.093	0.000	−1.705 to −0.481
Cerebrovascular accident	0.685	0.025	0.088 to 1.282
Tumour	−0.921	0.002	−1.490 to −0.352
Alcoholic	−0.286	0.031	−0.547 to −0.026
Number of interactions in which the route of the drug increased the manifestation of the interaction	−0.225	0.001	−0.352 to −0.099
Number of interactions in which the form of the drug increased the manifestation of the interaction	0.683	0.000	0.563 to 0.802
Number of interactions in which the dose of the drug increased the manifestation of the interaction R2=0.383; F (p)=17.669 (0.000)*	0.320	0.008	0.084 to 0.1556

*Statistically significant.
ATC, Anatomical Therapeutic Chemical; B, unstandardised coefficient; p, statistical significance.

have a protective attitude, while heart attack, cerebrovascular accident, dementia, rheumatic diseases, liver disease, diabetes mellitus, renal failure, dyslipidaemia and respiratory infection increase the risk of pDDIs. The same result was reached in a study conducted in the USA, except for hypertension, which was a protective factor.[27] It is obvious that there are variations with regard to the time and effort invested by prescribers in different areas of clinical practice.

The first limitation of our study is its unicentredness, which may introduce bias due to local and national peculiarities of medical education and practices. Second, since clinical outcomes of the patients related to the pDDIs could not be followed in our study, it is necessary to distinguish between potential and actual DDIs. Potential DDIs refer to a situation where two drugs that are known to interact are administered simultaneously, while the manifestation itself depends on the patient's characteristics and cannot be predicted with great certainty. Closer contact of pharmacologists and clinical pharmacists with patients is necessary, since only then a more detailed and accurate collection of information is possible, and the adverse outcomes of DDI are recognised more readily. More patients need to be included

in further research in order to enable generalisation of results and improvement of proactive measures for management and reduction of the risk of the occurrence of DDIs and undesirable outcomes of therapy.

CONCLUSIONS

Our study shows that DDIs are frequent in psychiatric inpatients, and one of the main drivers is polypharmacy. There are a number of sources of information on drug interactions that are available to healthcare professionals and that differ significantly from one another. It is essential that clinical pharmacists, physicians and nurses know how to use and evaluate the information provided by several electronic databases in making clinical decisions. Frequent detection of a large number of potential interactions, some of which may be of questionable clinical significance, leads to ignoring warnings about the possibility of drugs interacting, even those of great clinical significance. Current drug databases have many shortcomings, and there are many suggestions for their improvement, which include taking into account demographic, clinical and laboratory findings, as well as information on drug dosing regimens.[28] One needs to consult several interaction databases as well as have a multidisciplinary team consisting of an experienced clinical pharmacist, physician, nurse, and so on to reduce drug-related problems, including DDIs.

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